

WHAT IS CLAIMED IS:

1           1.       A method for screening a compound to determine whether the compound  
2 modulates immune cell signaling, the method comprising identifying a compound that  
3 modulates interaction between a PDZ protein and a PDZ ligand protein (a PL protein),  
4 wherein the PDZ protein and the PL protein are proteins which in an immune cell can interact  
5 with one another to affect the composition and/or distribution of lipid rafts in the immune  
6 cell.

1           2.       The method of claim 1, wherein identifying comprises  
2           (a)       contacting a PDZ domain polypeptide that comprises at least a partial  
3 sequence of the PDZ protein and a PL domain polypeptide that comprises at least a partial  
4 sequence of the PL protein in the presence of the compound; and  
5           (b)       determining whether there is a statistically significant difference in the  
6 amount of complex formed between the PDZ domain polypeptide and the PL domain  
7 polypeptide in the presence of the compound as compared to the amount of the complex  
8 formed in the absence of the compound, a statistically significant difference being an  
9 indication that the compound is a modulator of immune cell signaling.

1           3.       The method of claim 1, wherein the PDZ protein is selected from the group  
2 consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95, Pick1,  
3 CNK, GRIP and DVL-2.

1           4.       The method of claim 1, wherein the PL protein is selected from the group  
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na<sup>+</sup>/Pi  
3 transporter.

1           5.       The method of claim 1, wherein  
2           (a)       the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,  
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;  
4           (b)       the PDZ protein is TIP1 and the PL protein is LPAP or PAG;  
5           (c)       the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;  
6           (d)       the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or  
7           (e)       the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na<sup>+</sup>/Pi  
8 transporter.

1           6.       A method for modulating immune cell signaling, the method comprising  
2 modulating an interaction between a PDZ protein and a PDZ ligand protein (a PL protein),  
3 which interaction affects the composition and/or distribution of lipid rafts in an immune cell;  
4 and whereby such modulation alters immune cell signaling.

1           7.       The method of claim 6, wherein the PDZ protein is selected from the group  
2 consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95, Pick1,  
3 CNK, GRIP and DVL-2.

1           8.       The method of claim 6, wherein the PL protein is selected from the group  
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na<sup>+</sup>/Pi  
3 transporter.

1           9.       The method of claim 6, wherein  
2           (a)       the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,  
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;  
4           (b)       the PDZ protein is TIP1 and the PL protein is LPAP or PAG;  
5           (c)       the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;  
6           (d)       the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or  
7           (e)       the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na<sup>+</sup>/Pi  
8 transporter.

1           10.      The method of claim 6, wherein modulating comprises contacting an immune  
2 cell with a compound that inhibits or enhances interaction between the PDZ protein and the  
3 PL protein.

1           11.      The method of claim 10, wherein the compound includes a tetrazole moiety.

1           12.      The method of claim 10, wherein contacting comprises administering the  
2 compound to a patient having an immune disorder, the compound being administered in an  
3 amount effective to treat the immune disorder.

1           13.      The method of claim 12, wherein the immune disorder is an autoimmune  
2 disorder.

1           14.     The method of claim 12, wherein the immune disorder is selected from the  
2 group consisting of systemic lupus erythematosus (SLE), multiple sclerosis, diabetes  
3 mellitus, rheumatoid arthritis, inflammatory bowel syndrome, psoriasis, scleroderma,  
4 inflammatory myopathies, autoimmune hemolytic anemia, graves disease, Wiskott-Aldrich  
5 syndrome, lymphoma, leukemia, severe combined immunodeficiency syndrome (SCID) and  
6 acquired immunodeficiency syndrome (AIDS).

1           15.     The method of claim 10, wherein the compound enhances the interaction  
2 between the PDZ protein and the PL protein.

1           16.     The method of claim 10, wherein the compound inhibits the interaction  
2 between the PDZ protein and the PL protein.

1           17.     The method of claim 16, wherein the compound is  
2 (a)     a polypeptide or fusion polypeptide comprising a sequence that is from  
3 2 to about 20 residues of the C-terminal sequence of the PL protein;

4                 (b)     a polypeptide or fusion polypeptide comprising a sequence that is from  
5 2 to about 100 residues of the PDZ domain of the PDZ protein; or

6                 (c)     a small molecule mimetic of the polypeptide or fusion polypeptide of  
7 section (a) or (b).

1           18.     The method of claim 6, wherein the immune cell is a T-cell.

1           19.     The method of claim 6, wherein the immune cell is a B-cell.

1           20.     The method of claim 6, wherein the immune cell is a monocyte/macrophage.

1           21.     A modulator of binding of a PDZ protein and a PDZ ligand protein (a PL  
2 protein), wherein the modulator inhibits or enhances binding of a PDZ domain polypeptide  
3 and a PL domain polypeptide, and wherein

4                 (a)     the PDZ domain polypeptide comprises at least a partial sequence of  
5 the PDZ protein and the PL domain polypeptide comprises at least a partial sequence of the  
6 PL protein; and

7                 (b)     the PDZ protein and the PL protein are proteins which in an immune  
8 cell can interact with one another to affect the composition and/or distribution of lipid rafts in  
9 the immune cell.

1           22.     The modulator of claim 21, wherein the modulator is formulated as a  
2 pharmaceutical composition that comprises the modulator and a pharmaceutically acceptable  
3 carrier.

1           23.     The modulator of claim 21, wherein the modulator inhibits binding of the PDZ  
2 domain polypeptide and the PL domain polypeptide.

1           24.     The modulator of claim 21, wherein the modulator enhances binding of the  
2 PDZ domain polypeptide and the PL domain polypeptide.

1           25.     The modulator of claim 21, wherein the modulator is  
2           (a)     a polypeptide or fusion polypeptide comprising a sequence that is from  
3 2 to about 20 residues of a C-terminal sequence of the PL protein;  
4           (b)     a polypeptide or fusion polypeptide comprising a sequence that is from  
5 2 to about 100 residues of the PDZ domain of the PDZ protein; or  
6           (c)     a peptide or small molecule mimetic of the polypeptide or fusion  
7 polypeptide of section (a) or (b).

1           26.     The modulator of claim 21, wherein the PDZ protein is selected from the  
2 group consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95,  
3 Pick1, CNK, GRIP and DVL-2.

1           27.     The method of claim 21, wherein the PL protein is selected from the group  
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na<sup>+</sup>/Pi  
3 transporter.

1           28.     The method of claim 21, wherein  
2           (a)     the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,  
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;  
4           (b)     the PDZ protein is TIP1 and the PL protein is LPAP or PAG;  
5           (c)     the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;  
6           (d)     the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or  
7           (e)     the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na<sup>+</sup>/Pi  
8 transporter.

1           29.     The use of a modulator of the binding of a PDZ protein and a PDZ ligand  
2 protein (a PL protein) to treat an immune disorder, wherein the PDZ protein and the PL  
3 protein are proteins which in an immune cell can interact with one another to affect the  
4 composition and/or distribution of lipid rafts in the immune cell.

1           30.     The method of claim 29, wherein the PDZ protein is selected from the group  
2 consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95, Pick1,  
3 CNK, GRIP and DVL-2.

1           31.     The method of claim 29, wherein the PL protein is selected from the group  
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na<sup>+</sup>/Pi  
3 transporter.

1           32.     The method of claim 29, wherein  
2           (a)     the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,  
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;  
4           (b)     the PDZ protein is TIP1 and the PL protein is LPAP or PAG;  
5           (c)     the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;  
6           (d)     the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or  
7           (e)     the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na<sup>+</sup>/Pi  
8 transporter.

1           33.     The use of a modulator of the binding of a PDZ protein and a PDZ ligand  
2 protein (a PL protein) in the preparation of a medicament for treatment of an immune disease,  
3 wherein the PDZ protein and the PL protein are proteins which in an immune cell can interact  
4 with one another to affect the composition and/or distribution of lipid rafts in the immune  
5 cell.

1           34.     The method of claim 33, wherein the PDZ protein is selected from the group  
2 consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95, Pick1,  
3 CNK, GRIP and DVL-2.

1           35.     The method of claim 33, wherein the PL protein is selected from the group  
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na<sup>+</sup>/Pi  
3 transporter.

1           36.    The method of claim 33, wherein  
2                   (a)    the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,  
3    LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;  
4                   (b)    the PDZ protein is TIP1 and the PL protein is LPAP or PAG;  
5                   (c)    the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;  
6                   (d)    the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or  
7                   (e)    the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na<sup>+</sup>/Pi  
8    transporter.